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Acute renal failure in patients with rhabdomyolysis

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Summary

Background: Rhabdomyolysis is a relatively rare, not always diagnosed cause of acute renal failure (ARF). This fact motivated us to present the results of ARF treatment in the course of this polyetiological clinical syndrome.

Material/Methods: The analysis was performed on 84 patients (6 F, 78 M) ranging in age from 18 to 82 years (mean 46.5), in whom rhabdomyolysis was diagnosed based on clinical manifestation and laboratory test results (CPK, GTP, GOT, LDH).

Results: The most frequent cause of rhabdomyolysis was alcoholic intoxication (41 patients), often accompanied by hypothermia (15 patients) or trauma (30 patients). Isolated trauma was found in 30 patients, epileptic seizure in 5, and physical exercise in 1 case. In 17 patients, besides alcohol consumption, trauma or epileptic seizure, the use of tranquilizers, anticonvulsants, or narcotic drugs was additionally noted. 78 patients developed ARF requiring dialysis therapy; 49 patients recovered, 5 required maintenance dialysis, and 30 died.

Conclusions: During the initial phase of ARF in the course of rhabdomyolysis dynamic increases in serum urea and creatinine were observed, as well as a tendency to hyperkalemia. The treatment results and mortality rate in our study group were primarily influenced by the patients' general condition at admission, as well as the extent of organ damage caused by the primary etiological factor. Favorable treatment results were obtained especially in those patients who were hospitalized in a nephrological center, while the worst outcomes were noted in those patients dialyzed in intensive care units, most with multiple trauma.

Key words: hemodialysis • peritoneal dialysis

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BACKGROUND

Rhabdomyolysis is a relatively rare disease caused by various factors and characterized by skeletal muscle damage, which is manifested by elevated serum myoglobin level and myoglobinuria. The cause of muscle cell lysis is ischemia and acidosis. The diagnosis of rhabdomyolysis is based on clinical symptoms and signs, laboratory tests, and urinalysis results [1,2]. The clinical features of rhabdomyolysis include general and muscle weakness, increased body temperature, generalized or localized muscular pains, edema and tenderness on palpation [3–5]. This dangerous condition is relatively often complicated (in 30–80% of cases) by acute renal failure (ARF). The clinical course of rhabdomyolysis-caused ARF is similar to other forms. The causes, however, are entirely different. Among these, trauma (e.g. the crush syndrome) is of the greatest importance. Other significant factors include:
– ischemia;
– long lasting maintenance of a compulsory position (e.g. in coma, regardless of its cause, specialized surgical procedures);
– consumption of alcohol, narcotic drugs and other medications;
– CO intoxication;
– electrolyte imbalance [4,6–8].

Among non-traumatic factors that may contribute to rhabdomyolysis are congenital myopathies [9]. The drugs that may lead to rhabdomyolysis include sleeping pills, fibrates, HMG-CoA reductase inhibitors, narcotics, theophylline, pentamidine, colchicine and others that have attracted particular attention in the literature [4,10–12]. The biochemical features of rhabdomyolysis are closely associated with the degree of skeletal muscle damage and lysis. Muscle cell injury is typically manifested by an increased serum myoglobin level, myoglobinuria, significant values of CPK, GTP, GOT, LDH, hyperkalemia, and hyperuricemia [1,13]. Hypercalcemia in the initial phase of rhabdomyolysis is often accompanied by the deposition of calcium salts in soft tissues (mainly in skeletal muscles and myocardium), visible as metastatic calcifications [14,15]. The deterioration of renal function is connected with elevated serum urea and creatinine levels. A characteristic feature of this form of ARF is a disproportionately high increase in the creatinine level in relation to urea increase, with a BUN: creatinine [mg/dl] ratio $\leqslant$10. Urinalysis reveals dark color, granular casts, and epithelial cells present in the sediment, lack of significant erythrocyturia, with a simultaneous positive test for blood presence and myoglobinuria [1,3,5,13].

MATERIAL AND METHODS

The study was performed on 84 patients with rhabdomyolysis (78 M, 6 F), ranging in age from 18 to 82 years (mean 47.17), treated in the Department of Nephrology at the Jagiellonian University Hospital in Cracow, Poland, as well as in the intensive care units of other Cracow hospitals and in the regional hospital in Tarnów, Poland.

Rhabdomyolysis was diagnosed based on:
a) the presence of any of the etiological factors in the history (84 patients),
b) clinical symptoms:
   – body temperature over 37°C (67 patients),
   – signs of muscle injury (69 patients): edema, pain, muscular weakness,
c) changes in urinalysis:
   – dark colored urine (41 patients),
   – positive test for blood presence in urine without significant erythrocyturia in microscopic evaluation (50 patients),
d) pathological laboratory test results:
   – elevated serum CPK level above 500 U/l (84 patients),
   – elevated serum GOT, GTP, LDH (80 patients).

ARF was diagnosed in cases of oligoanuria and/or increased biochemical parameters of kidney function (serum creatinine above 2 mg/dl – 177 umol/l). At the same time, serum electrolytes and uric acid levels were measured, as well as blood cell count.

RESULTS

In our study group of patients with signs of rhabdomyolysis, we observed a tendency to rapid increases in serum urea and creatinine levels in the initial phase of ARF, as well as a relatively slow decrease after restoration of diuresis. In the acute phase, a tendency to hyperkalemia and hyperphosphatemia was also present. 56 patients developed hypocalcemia. which subsided quickly after restoration of diuresis. Three patients demonstrated transient hypercalcemia. Maximal CPK levels were observed in almost 70% of the cases on the first day of hospitalization. In another 30%, these peaks appeared on the second and consecutive days of treatment. In three cases, the CPK level remained increased for over 8 days.

The test results obtained in the initial period of treatment are presented in Table 1.

In our study group of patients, the causes of rhabdomyolysis were as follows:
– trauma (41 patients – 49%, including isolated injury in 26 cases, i.e. 31%),
– hypothermia (15 – 18%),
– seizures (14 patients – 17.1%, including epilepsy in 5 cases, 6%, and delirium tremens in 9 cases, 11%),
– excessive physical exertion (1 case, 1.2%),
– asthma attack (1 case, 1.2%),
– ethanol consumption (39 cases, 46%),
– drugs (sleeping pills, tranquilizers, anticonvulsants, antidepressants – 13 cases, 11%) and/or narcotic drugs (5 cases, 6%),
– CO intoxication (1 case – 1.2%).

In some patients, multiple causes were taken into consideration.

Among all the conditions contributing to ARF in the course of rhabdomyolysis, the dominant etiology was

Table 1. Results of the laboratory test values at admission.

Parameters	Mean	SD	Maximal value	Normal laboratory value
Ht (%)	35.75	12.5	55.0	40-54
Hb (g/dl)	11.02	5.8	19.0	13.5-15.5
RBC (mln/mm^3)	3.90	1.0	6.70	3.5-5.5
WBC (/mm^3)	14563	3954	28000	4000-10000
Platelets (/mm^3)	214000	108000	503000	200000-400000
CPK (U/l)	18829	23612	162644	up to 180
GOT (U/l)	971	1233	5920	up to 40
GTP (U/l)	586	650	4138	up to 40
LDH (U/l)	2513	3668	14325	up to
K (mmol/l)	5.74	1.09	8.6	3.5-5.5
Ca (mmol/l)	2.05	0.75	3.0	2.02-2.61
P (mmol/l)	2.18	1.44	4.5	0.87-1.45
Urea (mmol/l)	36.23	18.50	95.0	1.7-8.3
Creatinine (μmol/l)	649	315	1454	53-124
Uric acid (μmol/l)	614	197	1090	202-416

trauma (49%) and alcohol consumption (46%). Other interesting causes included excessive physical exertion connected with mowing the lawn, and an isolated asthma attack.

79 of our study patients developed full ARF requiring dialysis therapy. In 75 patients, ARF was accompanied by oligoanuria, lasting from 2 to 30 days.

Five patients with preserved diuresis required conservative treatment only (hydratation, forced diuresis, compensation for water-electrolyte and acid-base imbalance). In the other 79 patients, conservative treatment proved insufficient and dialysis therapy was introduced. 59 individuals underwent hemodialysis (HD), 3 had peritoneal dialysis (PD), and 13 had both HD and PD. The number of procedures performed ranged from 1 to 20 (mean 9.13). The most favorable results of treatment were achieved in 31 patients who fully recovered. Five patients (4M, 1F) required maintenance dialysis (4 HD, 1 PD), and 30 died (incl. 5 after restoration of diuresis).

The serum levels of the biochemical markers of renal function were the highest in the first few days of treatment. At the same time, the fastest dynamics of increase were found to be connected with hypercatabolism. A slow decrease after restoration of diuresis was also characteristic. Serum urea and creatinine levels did not correlate with the degree of muscle injury, as these are a sign of deterioration in kidney function and increased catabolism rate.

Discussion

The cases of rhabdomyolysis-caused ARF presented here formed a group of high heterogeneity. They differed not only in terms of the primary etiological factor, but most of all in the severity of the course and outcome of the pathological process, despite the application of a similar treatment regime. Great diversity was also observed in the clinical picture, as well as high dispersion in laboratory test results. Since the most common cause of rhabdomyolysis in our material was alcohol consumption, it is relatively easy to explain why men significantly outnumbered women in our study. Out of the four women, only in two cases could a causal link be established between rhabdomyolysis and alcohol consumption. The average age of the patients here described was relatively low (47.17 years), compared with other published results.

In all these patients elevated serum CPK values were found, which was the primary element of the diagnosis. As mentioned above, maximal CPK values were observed in 70% of the cases on the first day of hospitalization, a finding which is consistent with the results reported by other authors [1,15]. Normalization of this parameter was obtained in 81 patients within 4 to 7 days of treatment.

Hyperkalemia as a marker of cell lysis and excretory function damage appeared in all patients with oligoanuria, and required dialysis therapy. The initial tendency to hypocalcemia and hyperphosphatemia was probably caused by derangement in the synthesis and peripheral function of PTH, calcitonin, and the active form of vitamin D [15,16]. The normalization of these parameters followed the restoration of diuresis. Hypercalcemia was found in the initial phase of the disease in only two patients. In these same 2 patients focal lesions of metastatic calcification were found in skeletal muscles without myocardium involvement. This situation is noted in the literature as occurring in 10–20% of cases [14]. Serum CPK, GOT, GPT and LDH levels correlated with the extent of muscle damage. This finding had no prognostic value and has also been reported by other authors [1,13].

Among the factors contributing to rhabdomyolysis, two large groups may be distinguished: traumatic and non-traumatic. In as many as 45 of our patients, two or more etiological factors coexisted. The most frequent cause in the first group was injury. Rhabdomyolysis often resulted from hypothermia, usually connected with consumption of alcohol or narcotic drugs. 14 patients reported seizures. Among the relatively rarely reported and interesting cases we may note rhabdomyolysis-caused ARF in a patient after physical exertion (lawn mowing) and after an isolated asthma attack [17].

The action of the etiological factor (direct injury: compression, bruising, crush, blood vessel damage, excessive or insufficient oxygen supply in cases of excessive muscle reactivity) results in impaired/insufficient blood supply, and the attendant switch to anaerobic metabolism with intensive lactate production. This causes abnormal cell membrane permeability, followed by the release of inflammatory mediators and cell lysis.

The non-traumatic patients formed a very heterogeneous group. The etiological factors here were dominated by consumption of alcohol, medications, and/or narcotic drugs. Ethanol intoxication particularly entails water-electrolyte and acid-base imbalance, in the form of metabolic acidosis, hypomagnesemia, hypocalcemia,

ad hypophosphatemia. These are thought to take part in the pathomechanism of cell lysis [4,16–21]. Along with the compression caused by the extended maintenance of a compulsory position, direct narcotic drug toxicity and/or its contamination may play a role in the pathogenesis of rhabdomyolysis [7,12,17,18]. As for medications and other toxins, a distinction is made between their direct and indirect action (a predisposition to muscle cell lysis connected with their metabolism). It often occurs that both these mechanisms overlap [12,17,22,23].

From among the 84 patients described in this paper, only 5 did well on conservative treatment. This included compensation of water-electrolyte imbalance (administration of crystaloids, blood-derived products) and acid-base imbalance (pharmacological alkalization). Diuretics were administered simultaneously (mainly furosemide). The other patients required dialysis therapy in addition to symptomatic treatment. Since the patients differed in their overall clinical condition, the symptomatic management was relatively variable. Patients with multiorgan traumas (mainly crush syndrome) had full anti-shock treatment administered initially according to generally accepted regimes, and then important water-electrolyte and acid-base balance disturbances were corrected. After the patients' general condition had stabilized and ARF diagnosed, dialysis therapy was introduced. We did not use continuous venovenous hemofiltration, which is known to be especially efficient in removing myoglobin [26,27].

74 of the 81 patients with rhabdomyolysis-caused ARF also had oligoanuria, which lasted from 2 to 30 days. This is also consistent with the results reported by other authors, and justifies the formulation of a hypothesis, that rhabdomyolysis- caused ARF should not last for more than 30 days. Only sporadic cases have been reported with diuresis restoration after 35–48 days of treatment [12]. In our material, 30 patients (35.7%) died, including 5 after restoration of diuresis. These were mostly patients hospitalized in critical condition, with many etiological factors reported to be contributing to rhabdomyolysis, primarily multiple trauma. In 12 of these cases, anti-shock treatment failed. Thus it is not surprising that the mortality rate in this group was almost 90%.

CONCLUSIONS

In our study, the dynamics of serum urea and creatinine increases during the initial phase of ARF in the course of rhabdomyolysis were found to be very high, as well as a tendency to hyperkalemia. The treatment outcomes and mortality rate in our study group were mainly influenced by the patients' general condition at admission, as well as the extent of organ damage caused by the action of the etiological factor. Favorable treatment outcomes were obtained primarily in those patients who were hospitalized in a nephrological center, while the worst outcomes were noted in those patients dialyzed in intensive care units, mostly with multiple trauma.

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